REMARKS

Status of Claims

Claims 22-98 are pending in the present application. Claims 22-63, 65, 81, 82 and 98 are withdrawn. Claims 64, 66-80 and 83-97 are rejected.

By virtue of this response, claims 24-25, 27-31, 33-34, 37, 39-42, 44, 47-50, 55-63, 78, 83, 85, 87, 88, and 90-98 have been cancelled; claims 22, 45, 64, 67, 68, 75, 77, 80, 84, and 89 have been amended, without prejudice or disclaimer of any previously cancelled subject matter; and claims 99-133 have been added. After entry of these amendments, claims 22-23, 26, 32, 35-36, 38, 43, 45-46, 51-54, 64-77, 79-82, 84, 86, 89, and 99-133 will be pending and claims 22-63, 65, 81, 82, and 98 are withdrawn. No new matter has been added by the new or amended claims. Support for the claim amendments and additions is provided in detail below.

With respect to all amendments and cancelled claims, applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the patent office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional application.

Claim Amendments

Claims 22 and 64 have been amended to recite a composition comprising a plurality of conjugate wherein said conjugate is formable by the conjugation of an ethyleneoxide containing chemically defined valency platform molecule having specific structural features and a multiplicity of biologically active molecules.

The newly claimed features of the valency platform molecule include a moiety selected from $-CH_2(CH_2OCH_2)_rCH_2-$, 2,2'-ethylenedioxydiethylamine, triethylene glycol, and polyethylene glycol having a molecular weight of about 200 to about 8,000, wherein r = 0 to 300 and the moiety is derivatized with branching groups. Support for this claim feature is found, e.g., on page 4, lines

30-34 and from page 19, line 14 to page 20, line 9. Support for the particular derivatized moieties is found, e.g., on page 4, lines 31-34 and on page 20, lines 4-9 of the application as filed (also indicating a preference for ethyleneoxide-containing VPMs). Support for the moieties derivatized with branching groups is found, e.g., on page 19, lines 14-17. Applicants note that page 20, lines 3-9 recite valency platform molecules as "derivatized" moieties and page 19, lines 14-17 recite that branching groups are "added to" the platform molecules. Accordingly, the application as filed supports a claim reciting moieties derivatized with branching groups. Further support for these features can be found in Reactions Schemes 2 and 3, pages 32-33, which demonstrates 2,2'-ethylenedioxydiethylamine derivatized with branching group. Further support can also be found in Reaction Scheme 4 on page 34, which demonstrates triethylene glycol derivatized with branching groups. Further support can also be found in Reaction Scheme 7 on page 37, which demonstrates polyethylene glycol derivatized with branching groups. The reaction schemes noted above also disclose an ethyleneoxide containing moiety of the formula $-CH_2(CH_2OCH_2)_rCH_2-$ wherein r = 0 to 300 and the moiety is derivatized with branching groups.

Support for ethyleneoxide containing valency platform molecules is found throughout the specification as filed. The specification as filed fully describes valency platform molecules comprising ethyleneoxide, which is represented by the moiety $-O-CH_2-CH_2-O-$. For instance, Formula 2 on page 4 describes valency platform molecules comprising the moiety $-O-CH_2-CH_2-O-$ when component $G^{[2]}$ is of the formula $-CH_2(CH_2OCH_2)_rCH_2-$, wherein r = 0 to 300. Specifically, when r = 2, the resulting valency platform molecule comprises the moiety $-O-CH_2-CH_2-O-$ in the functional group $-CH_2CH_2-O-CH_2-CH_2-O-CH_2CH_2-$. In addition, page 20, lines 4-9 describe a valency platform molecule of derivatized 2,2'-ethylenedioxydiethylamine. A valency platform molecule of derivatized 2,2'-ethylenedioxydiethylamine comprises the moiety $-O-CH_2-CH_2-O-$. Particular examples of valency platform molecules of derivatized 2,2'ethylenedioxydiethylamine are exemplified in Reaction Schemes 2 and 3. The specification supports conjugates formable by the conjugation of biologically active molecules to ethyleneoxide containing valency platform molecules, as ethyleneoxide containing valency platform molecules are supported as shown above and in the disclosure of polymers of ethyleneoxide (e.g., PEG).

The claims also recite that "the valency of said platform molecule is provided by four or more attachment sites located at termini of the valency platform molecule." Support for this claim feature is found in part by the above-noted Reaction Schemes, as they all demonstrate four or more attachment sites that are at termini of the valency platform molecule. This feature is more generally supported by the formulae described, e.g., on pages 4-8 and 12-15. In these formulae, functional groups designated "T" are present at the termini of valency platform molecules. Example 3 on page 79, supports the general concept of reactive groups on valency platform molecules for conjugation, and Table 1, page 80 illustrates how various valency platform molecules can be synthesized with functional groups for conjugation, including functional groups shown as "T" in the Formulae 1 and 2. Conjugation of biologically active molecules to valency platform molecules takes place via attachment sites located on the valency platform molecule as described in even more detail, e.g., in the Modes for Carrying Out the Invention section of the specification, starting on page 17 of the application as filed. As such, the number of attachment sites provides the valency, as the attachment sites denote an upper limit to the number of biologically active molecules that may be conjugated to a single valency platform molecule.

Each of the newly claimed features of claims 22 and 64 is supported by the specification as filed. Accordingly, no new matter is added by amendment to claims 22 and 64.

Claim 45 has been amended to change DNA to the antecedent term polynucleotides.

Claims 67, 68, 77 and 84 have been amended to recite additional claim dependencies. Claims 67 and 68 are dependant on claims 64 and 66. Claims 77 and 84 are dependant on claims 64 and 74.

Claim 75 has been amended to change biologically active molecule to biologically active molecules as it is used in claim 64.

Claim 80 has been amended to reflect the amendment to claim 64, which recites polyethylene glycol having a molecular weight of about 200 to about 8,000.

Claim 89 has been amended to be multiply dependant on claims 64, 74, 80 or 84 and to recite that the conjugate comprise linking groups that bind the valency platform molecule to the biologically active molecules. This feature is supported by the previously presented claim, and the amendment presented herein merely replaces the language "bound to" with the phrase "that bind".

Claim 98 is withdrawn, but has been amended to recite the valency platform moieties presented in claim 64. Support for this amendment is as described for claim 64 above.

New Claims 99-131

New claims 99-105 are dependant claims directed to particular linking groups and attachment sites. Claims 99-100 recite various linker moieties and are supported in the application as filed, e.g., on page 9, lines 28-31; page 25, lines 5-21; Example 3, page 79 and Table 1, page 80. Claims 101-105 recite various attachment sites. Support for these claims can be found throughout the application as filed, e.g., in Example 3 starting on page 79,Table 1 on page 80, page 23, lines 7-9, and on page 25, lines 17-20.

New claims 106-128 are directed to conjugates formable by the conjugation of polynucleotides and an ethyleneoxide containing valency platform molecule.

Independent claim 106 is directed to a conjugate formable by the conjugation of a valency platform molecule having various structural features, and a polynucleotide. Support for this claim is found throughout the application as filed, e.g., from page 19, line 14 to page 20, line 9 and in the areas noted above for claim 64.

Dependant claim 107-111 are directed to various polynucleotides, and are supported in the specification as filed, e.g., on page 19, lines 29-32 (claim 107); e.g., page 22, lines 20-28; page 9, lines 20-27 (claim 108); e.g., page 22, line 34 to page 23, line 14 (claims 110-111).

Claim 112 is dependant on claim 111 and is directed to a composition suitable for reducing antibody levels. Support for this claim may be found, e.g., on page 10, lines 11-24, and in the examples starting on page 107.

Claim 113 is a dependant claim directed to conjugates wherein the polynucleotide is bound to the valency platform molecule via the 5' end of the polynucleotide. Support for this claim can be found throughout the specification, e.g., from page 22, line 29 to page 26, line 5.

Claim 114-118 are dependant claims reciting various linker group and are supported in the application as filed, e.g., on page 22, line 29 to page 23, line 14; page 25, lines 5-21. e.g., on page 9, lines 28-31.

Claims 119-123 are dependant claims directed to various attachment sites. Support for these claims can be found throughout the application as filed, e.g., in Example 3 starting on page 79,Table 1 on page 80, page 23, lines 7-9, and on page 25, lines 17-20.

Claims 124-125 are dependant claims directed to conjugates in a pharmaceutical composition and formulated with a pharmaceutically acceptable injection vehicle. These claims are supported, e.g., on page 29, lines 25-35.

Claim 126 is a dependant claim reciting a tolerogen. Support for this amendment may be found, e.g., on page 29, lines 21-25 and in the examples starting on page 107.

Claim 127 is a dependant claim reciting a conjugate suitable for the treatment of human system lupus erythematosis, and is supported, e.g., on page 9, lines 1-27 and in the examples starting on page 107.

Claim 128 is directed to a method of making the conjugate of claim 107, and is supported, e.g., on page 11, lines 20-31.

Claim 129 is directed to a method of making the conjugates of claims 64 or 106 and is supported by previously presented claim 44.

Claims 130 and 131 are directed to specific embodiments selected from the Markush group of the parent claim 64.

Applicants' representative notes with appreciation the Examiner's withdrawal of the previously-imposed rejections based on the references, on obviousness double-patenting, and on 35 U.S.C. Sec. 112 first paragraph grounds as recited on page 2 of the Office Action. The Office Action notes on page 2 though that some of the previous obviousness double-patenting rejections were maintained. These double-patenting rejections relate to claims withdrawn from consideration. Applicant's representative therefore provides no comments on the rejection of the withdrawn claims, since such comments would be moot.

Obviousness double patenting

U.S. Patent No. 5,276,013

Claim 64 stands rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claim 1 of U.S. Patent No. 5,276,013. Applicants respectfully traverse the rejection.

Claim 1 of U.S. Patent No. 5,276,013 recites a conjugate of a biologically stable valency platform molecule and a multiplicity of polynucleotide duplexes. Claim 1 of U.S. Patent No. 5,276,013 does not suggest conjugates with the specific structural characteristics recited in claim 64 of the instant application. In particular, there is no suggestion in claim 1 of U.S. Patent No. 5,276,013 of a conjugate formable by the conjugation of biologically active molecules to a valency platform molecule comprising particular chemical moieties derivatized with branching groups, wherein the valency is provided by four or more attachment sites located at termini of the valency platform molecule. The specific structural characteristics recited in claim 64 render claim 64 patentably distinct from claim 1 of U.S. Patent No. 5,276,013.

The Office Action states that "[i]t is true that claim 1 of '013 does not suggest that the VPM should be branched. However, since claim 1 of USP '013 is silent on the matter of branching, it encompasses both. Perhaps it can be argued that if claim 1 of the patent were considered in a vacuum, one could not be certain that the claim encompassed the invention that is defined by (instant) claim 75. But it is entirely appropriate to consider the contents of the description (of the invention) in endeavoring to assess that which may be encompassed."

The rejection appears to be based in two premises from the explanation at pages 3-4 of the Office Action. The first premise appears to be that because an earlier claim may include species within its scope, a claim in a later-filed application to that species may be rejected for obviousness-type double patenting. The premise, in other words, is that if a claim in an issued patent dominates a claim in a later application, the claim in the later application is obvious.

The Office Action on pages 3-4 also states that it is entirely appropriate to consider the contents of the description of the invention in U.S. Patent No. 5,276,013 when assessing the subject matter that is encompassed by claim 1 of that patent. The Office Action notes in particular the valency platform molecule depicted at the top of columns 17 and 18 of U.S. Patent No. 5,276,013 and states that a conjugate of this valency platform molecule meets all the limitations of instant claim 64, and this conjugate is within the scope of claim 1 of U.S. Pat. No. 5,276,013. The comments also note in particular that claim 1 of U.S. Pat. No. 5,276,013 is silent on whether the VPM should be branched.

This rejection therefore appears to be based in a second premise, that a species (1) which is disclosed in a patent specification, (2) which is within the scope of a generic claim, and (3) which is not otherwise suggested by that generic claim, may be used to reject a later-filed patent claim that also claims that species under the doctrine of obviousness-type double patenting. Both premises are incorrect.

The second premise in essence treats a portion of the disclosure of Applicants' U.S. Patent No. 5,276,013 as prior art to claim 64 of the pending application. However, "when

considering whether the invention defined in a claim of an application is an obvious variation of the invention defined in the claim of a patent [under the doctrine of obviousness-type double-patenting], the disclosure of the patent may not be used as prior art." Manual of Patent Examining Procedure, Eighth Ed., §804.

Confirming the improper use of a patent disclosure in this context, the U.S. Court of Appeals for the Federal Circuit stated that an obviousness-type double patenting rejection that treats the patent specification as though it were prior art "has repeatedly been held in our precedents to be impermissible" *In re. Kaplan, 789 F.2d 1574, 229 USPQ 678* (Fed. Cir. 1986). *In re. Kaplan* concerned an issued patent and a subsequent application, where the issued patent claimed a genus and the subsequent application under examination claimed an improvement species thereof. The improvements claimed in the species application were disclosed and were within the scope of the genus claims of the patent but were not specifically claimed in the issued patent.

In reversing the obviousness type double patenting rejection, the Federal Circuit focused on two main errors: (1) the rejection confused claim domination with obviousness type double patenting, and (2) the rejection had attempted to incorporate the specification of the issued patent into the obviousness double patenting analysis.

In re. Kaplan indicates that claims under examination cannot be rejected for obviousness-type double patenting under the rationale that the examined claims are dominated by earlier issued patent claims. No improvement patents could ever issue to anyone other than the patentee if the law was otherwise. *In re. Kaplan* also indicates (1) it is impermissible to use a species disclosed in the issued patent and within the scope of generic claims of the earlier patent to reject claims in a later patent application for obviousness-type double patenting, and that (2) the correct comparison for an obviousness-type double patenting rejection is to determine if the later set of claims is obvious in view of the earlier-issued claims, even though the later-claimed species might be within the scope of the earlier-issued claims and even though the later-claimed species is disclosed in the specification of the earlier patent.

The rejection of claim 64 over claim 1 of U.S. Patent No. 5,276,013 is based in an incorrect rationale that a species within the scope of a genus claim that is disclosed in the specification of an earlier-issued patent can be used to reject claims in a later-filed patent application. The notion that examples disclosed in the specification of an earlier genus patent provide support for an obviousness-type double-patenting rejection of later-filed claims to species directed to those examples was rejected by *In re. Kaplan. In re. Kaplan* forbids using the single compound disclosed in the specification U.S. Patent 5,276,013 to reject claim 64 of the instant application as being obvious from claim 1 of U.S. Patent No. 5,276,013. The Office Action has also stated that claim 1 of U.S. Pat. No. 5,276,013 does not suggest all of the features of claim 64 of the instant application. Claim 64 is therefore not obvious from claim 1 of U.S. Pat. No. 5,276,013. Applicants respectfully request withdrawal of the rejection.

U.S. Patent No. 6,060,056

Claim 64 is rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claim 1 of U.S. Patent No. 6,060,056. Applicants respectfully traverse the rejection. Claim 1 of U.S. Patent No. 6,060,056 claims a conjugate comprising a nonimmunogenic valency platform molecule and analog molecules having certain characteristics specified in the claim. Claim 64 of the instant application claims a conjugate formable by the conjugation of an ethyleneoxide containing valency platform molecule having specific structural features such as four or more attachment sites located at termini of the valency platform molecule. Claim 1 of U.S. Patent No. 6,060,056 does not suggest a conjugate formable by the conjugation of an ethyleneoxide-containing chemically defined valency platform molecule having the structural features of amended claim 64 and biologically active molecules. The subject matter of instant claim 64 is not obvious in view of the broad recitation of a "nonimmunogenic valency platform molecule" in claim 1 of U.S. Patent No. 6,060,056, and Applicants assert that claim 64 in the instant application is therefore patentably distinct from claim 1 of U.S. Patent No. 6,060,056.

In levying the present rejection, the Office Action points to the disclosure of the molecule at column 13, line 27 of U.S. Patent No. 6,060,056 to maintain the rejection of instant claim 64. The Office Action also states that there is overlap in the claims that justifies a double-patenting rejection.

As noted above, "when considering whether the invention defined in a claim of an application is an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art." Manual of Patent Examining Procedure, Eighth Ed., §804. *In re. Kaplan* also cautions against confusing claim overlap, as occurs with a genus dominating a species as occurred in *Kaplan*, with the issue of whether the language of a claim specifying the claimed subject matter in an earlier-issued patent renders obvious later-claimed subject matter. The particular compound noted by the Examiner cannot in effect be treated as prior art and used as a basis for the obviousness-type double patenting rejection under *In re. Kaplan*, and Applicants respectfully request withdrawal of the rejection.

U.S. Patent No. 5,552,391

Claim 64 is rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claim 1 of U.S. Patent No. 5,552,391. Applicants submit that this issue will be addressed upon obtaining otherwise allowable subject matter..

U.S. Application Serial Number 09/753,350

Claim 64 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 22 and 32 of U.S. Serial No. 09/753,350. In response, Applicants respectfully note the provisional nature of the rejection and submit that this issue will be addressed upon obtaining otherwise allowable subject matter.

U.S. Application Serial No. 09/509,592

Claims 64, 78 and 80 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 46 of U.S. Serial No. 09/509,592. In response, Applicants respectfully note the provisional nature of the rejection and submit that this issue will be addressed upon obtaining otherwise allowable subject matter.

Rejections under 35 USC § 112, first paragraph

Claims 64, 66-77, 79 and 83-97 are rejected under 35 USC § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner suggests descriptive support is lacking because the claims recite a conjugate formable by the reaction of biologically active molecules with a valency platform molecule comprising the functional group $-O-CH_2-CH_2-O-$.

Applicants submit that the issue is moot due to the claim amendments. Claims 87, 88 and 90-97 have been cancelled, and Applicants have amended claims to better state the claimed subject matter. The language reciting the moiety $-O-CH_2-CH_2-O-$ has been removed from claim 64. Claim 64 has been amended to recite an ethyleneoxide containing chemically defined valency platform molecule comprising a moiety selected from $-CH_2(CH_2OCH_2)_rCH_2-$, wherein r = 0 to 300, 2,2'-ethylenedioxydiethylamine, triethylene glycol, and polyethylene glycol having a molecular weight of about 200 to about 8,000. Claim 64 as amended is fully supported by the application as filed, as described in detail under the AMENDMENTS TO THE CLAIMS section of this response.

Applicants submit that the amendments to claim 64 have also addressed the objection to claims 81 and 82 as well as the other claims not specifically discussed in the office action, as the subject matter claimed in claims 81 and 82 is described as preferred. Applicants respectfully request that the examiner withdraw the § 112, first paragraph rejection of claim 64, 66-77, 79, 83-86 and 89.

Rejections under 35 USC § 112, second paragraph

Claims 81and 82 are rejected as being indefinite under 35 USC § 112, second paragraph because claims 81 and 82 are dependant on a non-elected claim. The Examiner has acknowledged that claims 81 and 82 are withdrawn and has designated them withdrawn on the Office Action Summary. Applicants therefore will address any remaining issues with respect to claims 81 and 82 upon rejoinder and examination.

Rejections under 35 USC § 103

U.S. Patent No. 4,820,812

Claims 64, 68 and 71 are rejected under 35 USC § 103 as allegedly being unpatentable over Miyoshi (U.S. Patent No. 4,820,812). Applicants assert that the claims 64, 68 and 71 are not rendered obvious over U.S. Patent No. 4,820,812.

U.S. Patent No. 4,820,812 is in the field of chromatography and concerns the development of immobilized oligonucleotides and their use in purification methods and in affinity resins. The teachings of U.S. Patent No. 4,820,812 are outside Applicants' technical field of endeavor. The Office Action does not suggest what the motivation is for one of ordinary skill to look to the field of chromatography or specifically to the teachings of U.S. Patent No. 4,820,812 in the development of conjugates of biologically active molecules and chemically defined valency platform molecules for use in treating disease. The claims cannot be rendered obvious by a teaching outside the technical field of the present invention without specific motivation to be steered toward such reference. Accordingly, the claims under this rejection are not rendered obvious by the chromatographic teachings of U.S. Patent No. 4,820,812.

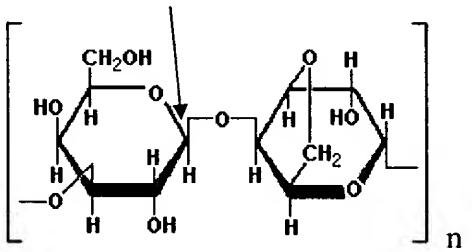
Applicants in addition address the chromatographic teachings of U.S. Patent No. 4,820,812 in the comments that follow.

As stated by the Examiner, U.S. Patent No. 4,820,812 discloses oligonucleotides bonded to sepharose, which is a polysaccharide polymer of agarose. The Examiner states that oligonucleotides bonded to sepharose meet the limitations of the instant claims because the anomeric carbon of a polysaccharide, together with the atoms adjacent thereto, comprise the moiety $-O-CH_2-CH_2-O-$ and that the resulting structure is within the scope of the claim 64. Applicants respectfully disagree.

Although the claims do not specifically recite the moiety $-O-CH_2-CH_2-O-$ any longer, Applicants address the rejection because the present claims encompass compositions having an ethylene oxide moiety such as $-CH_2-CH_2-O-$ or $-O-CH_2-CH_2-O-$. For sake of conciseness, the following paragraphs discuss only the $-O-CH_2-CH_2-O-$ moiety, but the arguments also apply to the moiety $-CH_2-CH_2-O-$.

Applicants believe that a polysaccharide, and agarose in particular, does not comprise the moiety $-O-CH_2-CH_2-O-$. Applicants also assert that an anomeric carbon of a saccharide cannot be represented as HO-CH-C(O)O, as the Examiner suggests. Applicants further contend that even if a saccharide comprised the structure HO-CH-C(O)O as suggested by the Examiner, this moiety does not comprise $-O-CH_2-CH_2-O-$.

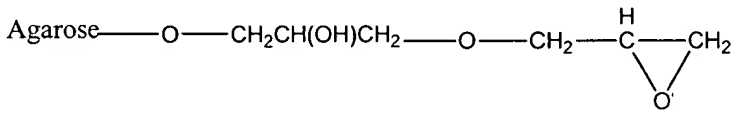
The repeating disaccharide of agarose is shown in the structure below, where the anomeric carbon is identified by the arrow.



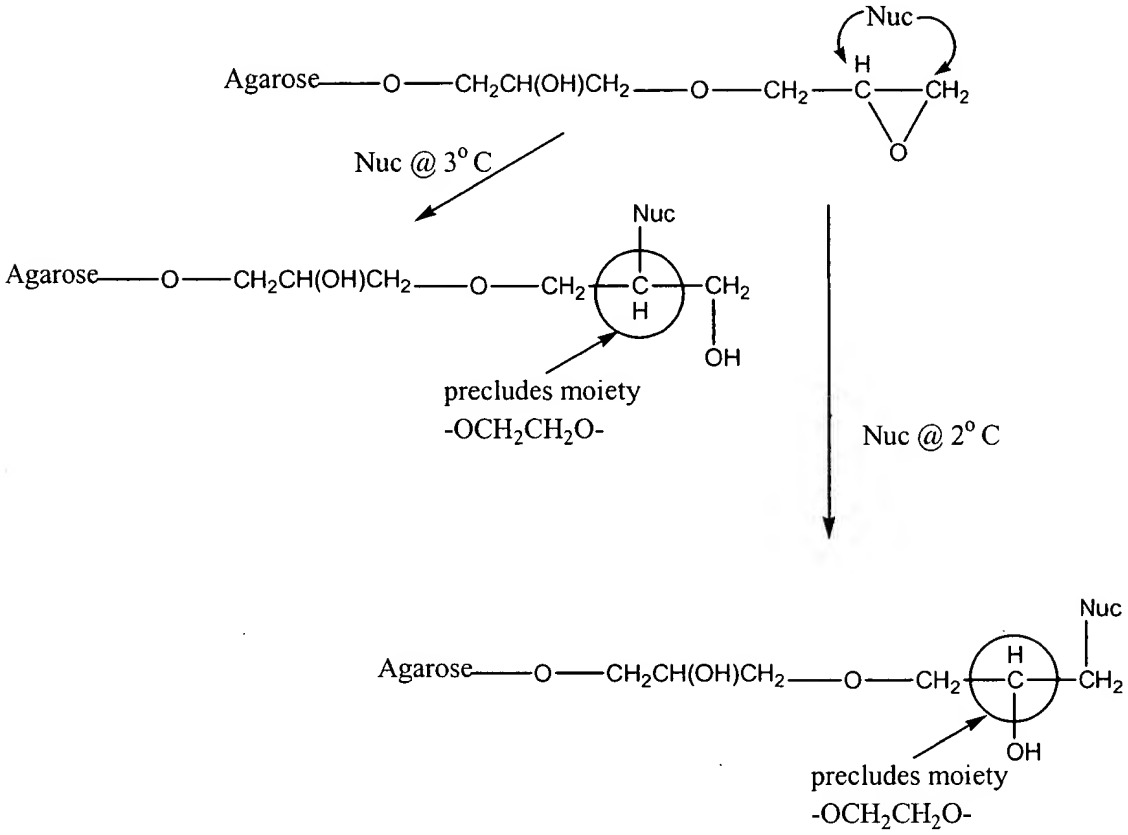
The moiety $-O-CH_2-CH_2-O-$ is not found anywhere within the disaccharide structure of agarose, and not at the location of the anomeric carbon as suggested by the Examiner. The anomeric carbon of the disaccharide does not give rise to a moiety of the formula $-O-CH_2-CH_2-O-$

because the anomeric carbon is a tetracoordinated carbon bound to four atoms, only one of which is a hydrogen. It would be necessary to open the ring structure and bond a hydrogen to the anomeric carbon atom to obtain a moiety of the formula $-O-CH_2-CH_2-O-$. This would certainly not be an obvious variant of what is disclosed in the reference, as there is no suggestion to open one of the ring structures of agarose at the anomeric carbon atom. A conjugate comprising agarose and a multiplicity of biologically active molecules therefore does not suggest the conjugates recited in claims 64, 68 or 71 because agarose does not comprise or suggest the moiety $-O-CH_2-CH_2-O-$ or otherwise suggest the subject matter of the amended claims.

In connection with the rejection of claims 64, 68 and 71 over U.S. Patent No. 4,820,812, the Examiner suggests the moiety $-O-CH_2-CH_2-O-$ arises upon reaction of an epoxidized sepharose with a nucleophile. Applicants respectfully disagree. The epoxidized sepharose disclosed at column 9, line 55 of U.S. Patent No. 4,820,812 is reproduced below.



The Examiner suggests that the above epoxide, upon reaction with a nucleophile, will comprise the moiety $-O-CH_2-CH_2-O-$. Applicants assert that the structure resulting from an epoxide opening reaction will *not* comprise the moiety $-O-CH_2-CH_2-O-$, whether the epoxide opens at the secondary carbon or the tertiary carbon. Applicants describe an epoxide-opening reaction as suggested by the Examiner in the following reaction diagram, and indicate the reaction products of nucleophilic attack at the secondary and tertiary epoxide carbons.



As shown above, an epoxidized agarose of U.S. Patent No. 4,820,812 having undergone nucleophilic attack will not comprise a moiety of the formula –O-CH_2-CH_2-O- because the carbon noted by the arrow above precludes successive CH_2 groups which are present in ethyleneoxide. Accordingly, neither agarose nor epoxidized agarose in its opened form comprise ethyleneoxide (–O-CH_2-CH_2-O-) or suggest a conjugate of biologically active molecules and an ethyleneoxide containing valency platform molecule as recited in amended claim 64.

For the reasons explained above, U.S. Patent 4,820,812 does not suggest the conjugates claimed in claims 64, 68 or 71. Applicants respectfully request withdrawal of the rejection of claims 64, 68 and 71 over U.S. Patent No. 4,820,812.

U.S. Patent 4,904,582 in view of Lehninger (pages 742-743)

Claims 64, 67, 68, 78, 80 and 83 are rejected under 35 USC § 103 as allegedly being unpatentable over Tullis (USP 4,904,582) in view of Lehninger (pages 742-743).

The Examiner states that U.S. Patent No. 4,904,582 discloses a polynucleotide which bears a polyethylene glycol at the 5'position, represented by X-Y-L-Z (terminal polynucleotide-internal polynucleotide-linker-PEG). The Examiner alleges that the claims under this rejection are rendered obvious because the compounds of U.S. Patent No. 4,904,582 may be considered a conjugate of a "valency platform molecule" in the form of Y-L-Z (internal polynucleotide-linker-PEG) moiety and "biologically active molecules" in the form of four nucleotide bases at the 5' end, along with the terminal polynucleotide fragment designated "X" and that Lehninger (pages 742-743) teaches nucleotide bases are biologically active molecules. Applicants assert that the compounds of U.S. Patent No. 4,904,582 do not render obvious claim 64 as amended or the dependant claims thereof.

Claim 64 as amended recites conjugates of an ethyleneoxide containing chemically defined valency platform molecule and requires the valency of the platform molecule to be provided by four or more attachment sites *located at termini of the valency platform molecule.* The molecules disclosed in U.S. Patent No. 4,904,582 are oligonucleotides bound to a PEG moiety. If the oligonucleotides of the '582 patent are viewed as suggest by the Examiner, the "multiplicity of biologically active molecules" are the individual nucleotide bases of the oligonucleotide polymer. As such, both the "terminal nucleotide" and all "internal nucleotides" comprise nucleotide bases. However, if the nucleotide bases are attached to what the Examiner is suggesting is the "valency platform molecule," the nucleotide bases are attached along the entirety of the oligonucleotide polymer. As such, the attachment sites for biologically active molecules are located at each internal nucleotide as well as at one terminal nucleotide. The '582 patent therefore does not disclose a conjugate having four or more attachment sites located at termini of the valency platform molecule that may be conjugated to biologically active molecules. There is only one terminal attachment site, the one furthest in the chain of |P(X)Z| moieties from linker L.

The secondary reference, Lehninger, likewise fails to suggest four or more terminal attachment sites. Accordingly, claims 64, 67, 68, 78, 80 and 83 are not obvious over the U.S. Patent No. 4,904,582 in view of Lehninger (pages 742-743) because the references, when combined, fail to disclose all features of Applicants' claimed subject matter.

Applicants respectfully request withdraw of the rejection of claims 64, 67, 68, 78, 80 and 83 under 35 USC § 103 as allegedly being unpatentable over Tullis (USP 4,904,582) in view of Lehninger (pages 742-743).

U.S. Patent No. 4,567,422

Claims 64, 67, 68 and 78 are rejected under 35 USC § 103 as allegedly being unpatentable over Greenwald (USP 4,567,422).

The Examiner asserts that U.S. Patent No. 4,567,422 discloses conjugates of azlactone-derivatized PEG and oligonucleotides and that such conjugates render obvious claims 64, 67, 68, and 78. The Examiner makes several assertions with regard to this rejection, including (1) that one of ordinary skill would reason the an azlactone-derivatized PEG of U.S. Patent No. 4,567,422 will react with nucleotide bases at various points along the structure of the oligonucleotide and that the resulting conjugate structure will be branched; (2) the biologically active molecules of such conjugates are terminal fragments of oligonucleotides and ethyl alcohol; (3) that PEG contains biologically active molecules because it is a polymer of recurring ethanol units; and (4) that if the azlactone-derivatized PEG were to react with a 'middle' nucleotide of a larger chain oligonucleotide, the result would be a branch point, thereby satisfying the requirements of claim 68.

There is no suggestion in U.S. Patent No. 5,567,422 of conjugates formable by the conjugation of biologically active molecules to ethyleneoxide containing valency platform molecules wherein the valency is four or more. As stated in column 5, lines 34-37 of U.S. Patent No. 5,567,422, "when the moieties selected for L and R1 on both ends of the polymer are identical, the polymer will then be a symmetrical, *homobifunctional* polymer derivative." Thus, the maximum valency for the azlactone-derived PEG's of U.S. Patent No. 5,567,422 is two. The azlactone-derivatized PEG platform molecules with a maximum of two attachment sites for

biologically active molecules do not suggest the conjugates of the instant claims, which require the valency platform molecules to have four or more attachment sites.

Applicants respectfully request that the examiner withdraw the rejection of claims 64, 67, 68 and 78 under 35 USC § 103 as allegedly being unpatentable over Greenwald (USP 4,567,422).

U.S. Patent No. 5,451,576

Claims 64, 66, 67, 78 and 80 are rejected under 35 USC § 103 as allegedly being unpatentable over Sessler (USP 5,451,576). U.S. Patent No. 5,451,576 is directed to hydroxyl derivatives of texaphyrin. The Examiner has indicated that the two compounds in Figure 11C of U.S. Patent No. 5,451,576 render the claims obvious. Applicants respectfully disagree.

When assessing whether claimed subject matter is obvious under 35 U.S.C. Sec. 103(a) in view of a reference, it is applicant's representative's understanding that the office is to assess what a reference teaches, not what someone might possibly have done to derive the subject matter disclosed in the reference. Applicants submit that the office action has utilized an incorrect approach in analyzing whether the claimed subject matter is unpatentable under U.S.C. Sec. 103(a). The office action speculates that the compound of Figure11C of the Sessler '576 patent could have been formed by a method as described in the office action, but the reference does not teach the method described in the office action, and the compound disclosed in Figure 11C of the Sessler '576 patent certainly does not suggest applicants' claimed subject matter.

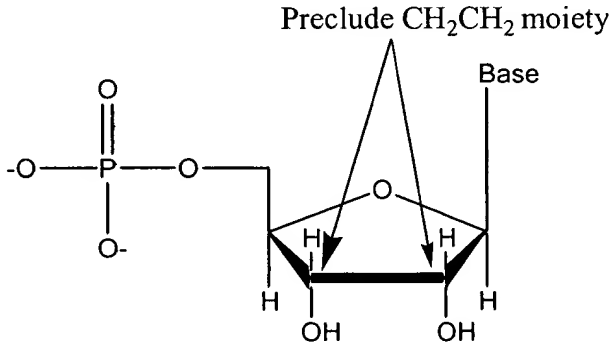
Applicants submit that the rejection has gone far beyond what one of ordinary skill would view as the biologically active molecule in this reference. Applicants submit that the texaphyrin is the biologically active molecule, not the hydroxyl groups on the texaphyrin that appear from the cited reference to be added to the texaphyrin to increase solubility of the texaphyrin. Viewed in this manner, it is quite plain that the '576 patent does not disclose multiple biologically active molecules conjugated to terminal attachment sites, of which there are four or more attachment sites.

Applicants respectfully request that the examiner withdraw the rejection of claims 64, 66, 67, 78 and 80 under 35 USC § 103 as allegedly being unpatentable over Sessler (USP 5,451,576).

Datta, Banisdhar (J. Biol. Chem. 267(7), 4497-502, 1992) or Osswald, Monika (Nucleic Acids Research 18(23), 6755-60, 1990) or Doering, Thomas (Nucleic Acids Research 19(13), 3517-24, 1991).

Claims 64, 67, 78 and 70 are rejected under 35 USC § 103 as allegedly being unpatentable over Datta, Banisdhar (J. Biol. Chem. 267(7), 4497-502, 1992) or Osswald, Monika (Nucleic Acids Research 18(23), 6755-60, 1990) or Doering, Thomas (Nucleic Acids Research 19(13), 3517-24, 1991). As noted by the Examiner, each of the references used in this rejection disclose crosslinked RNA. The Examiner contends that crosslinked RNA is a conjugate between a valency platform molecule and a biologically active molecule and that the structural requirement of $-O-CH_2-CH_2-O$ is met by the pentose units of RNA. Applicants respectfully disagree.

As an initial matter, a pentose unit of RNA does not comprise the functional group $-O-CH_2-CH_2-O-$. A pentose unit of RNA, as properly noted by the Examiner, is of the formula:



However, nowhere in the pentose unit is there a moiety of $-O-CH_2-CH_2-O-$. The carbons bearing the OH groups of the pentose ring are not unsubstituted CH_2 moieties, and by virtue of their presence in a ring structure, preclude the presence of a CH_2CH_2 moiety. Claim 64 as amended requires the presence of an ethyleneoxide containing valency platform molecule with particular

structural features. RNA is not an ethyleneoxide containing molecule and does not render obvious amended claim 64 or the dependant claims thereof. In addition, RNA lacks the additional structure features of amended claim 64, such as four of more attachment sites located at termini of the platform molecule. For these reasons, Datta, Banisdhar (J. Biol. Chem. 267(7), 4497-502, 1992) or Osswald, Monika (Nucleic Acids Research 18(23), 6755-60, 1990) or Doering, Thomas (Nucleic Acids Research 19(13), 3517-24, 1991) do not suggest the conjugates as claims. Applicants respectfully request withdrawal of the 35 USC § 103 rejection in connection with these references.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no.252312005704. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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